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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,933	12/31/2003	Dilip G. Saoji	U 014338-7	6675

7590 09/22/2006

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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,933	SAOJI ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *22-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Acknowledgement is made of Applicants claim for foreign priority under USC 119(a)-(d) filed December 31, 2002.

Response to Restriction Election

The response filed **July 17, 2006** presents remarks and arguments to the office action mailed **April 13, 2006**. Applicant's election with traverse of Group I, Claims 1-21 in the reply is acknowledged. Claims 22-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed. The traversal is on the ground(s) that All rights to file one or more divisional applications directed to the subject matter of the nonelected claims and/or any other subject matter disclosed in the specification are preserved. However, Applicant did not traverse per se the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 1-21 are elected and are pending in this office action.

Claims 22-37 are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics

coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" for the retinoid means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

In other words, the Applicant has not described with sufficient clarity a retinoid contemplated is not described nor exemplified and does not inform the public of limits of the monopoly asserted.

The above rejection is also applied to the anti-bacterial, a steroid/non-steriod anti-inflammatory agent and antifungal agent or mixtures thereof in claim 1.

II. Claim 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The compound structure of formula I does not specify or give the possible substituents of every prodrugs that possibly exist does not inform the public of the limits of the monopoly asserted.

III. Claims 1-21 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts, does not reasonably provide enablement for making prodrugs of the claimed compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

the quantity of experimentation necessary

Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound

metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

the presence or absence of working examples

There is no direction in the specification concerning produgs, there are no working examples for a prodrug of a compound of formula I.

The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body., e) Wolff

(Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is

particularly relevant. Banker (Modem Pharmaceutics) Banker, G.S. et al, "Modem Pharmaceutics, 3ed.",Marcel Dekker, New York, 1996, pages 451 and 596. The first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug, f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph.D. degree and several years of industrial experience.

The breadth of the claims includes numerous of the hundreds of thousands of compounds of formula.

undue experimentation will be required to determine if any particular benzoquinolizine- 2-carboxylic acid is, in fact, a prodrug.

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compound. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions of how to make such a compound.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim **1 - 9** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1 - 12** of U.S. Patent No. 6514986 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

> Both sets of claims refer to treating the same identical compounds used in a composition for treating antimicrobial infections. The current application claims are obvious variation of the patented claims
>
> Both applications recite using the same compositions and/or derivatives thereof. See current application claims 1 - 9 and patented claims 1 – 12.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

Claim **1 - 9** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1 - 3** of U.S. Patent No. 6608078 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

> Both sets of claims refer to treating the same identical compounds used in a composition for treating antimicrobial infections. The current application claims are obvious variation of the patented claims
>
> Both applications recite using the same compositions and/or derivatives thereof. See current application claims 1 - 9 and patented claims 1 -3

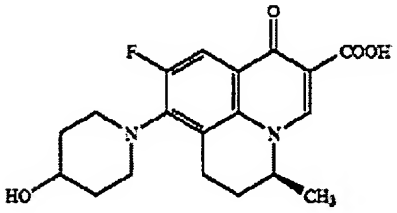
In view of the foregoing, the copending application claims and the current application claims are obvious variations

Claim Rejections - 35 USC § 102

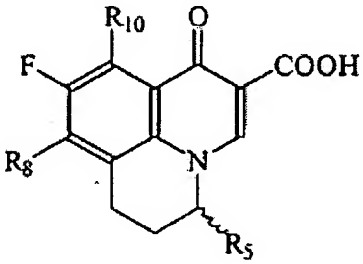
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6 and 20-21 are rejected under 35 U.S.C. 102(e) as being anticipated by de Souza et al. US 6,514,986.

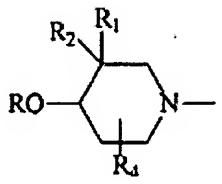
De Souza et al. teach a stable pharmaceutical composition comprising an aqueous carrier having in solution therein a benzoquinolizine-2-carboxylic acid



having the core chemical structure



as that disclosed in the instant claim1 (see col. 4, lines 15+) that is an optical active isomer, in a pharmaceutically acceptable salt arginine singly or combined with other antibacterial agents (see col. 8, lines 32+). With regards

to claim 2 R_5 is CH_3 and R8 is  is shown in the above structure, where R_1, R_2 R_4 are hydrogen. As to claims 3 and 6 the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin- 1-yl)-5-methyl- 1-oxo- 1H,5H- benzo(ij)quinolizine-2-carboxylic acid and the arginine salt form in claim 4 (see col. 5 lines 20+), where in the drug is 0.2 hydrate is anticipated since the hydrate forms are from 0 to 1.0(see col. 4 lines 30) as in current claim 5 wherein the pharmaceutically acceptable salt if from an acid (see col. 2, lines 1+) as in claim 20 having a physical form of a cream (see col. 8, lines 35+)as in claim 21.

Claims 1-6 and 20-21 are rejected under 35 U.S.C. 102(e) as being anticipated by de Souza et al. US 6,608,078 B.

With regards to claim 1, the reference teaches a stable pharmaceutical composition having the core structure of the claimed invention (see col. 5, lines 25+), with the substituent or a polymorphs and pseudopolymorphs (see abstract) as in claim 1and 4, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin- 1-yl)-5-methyl- 1-oxo- 1H,5H-benzo(ij)quinolizine-2-carboxylic acid and the arginine salt form in claim 4 (see col. 8 lines 11+) wherein the pharmaceutically acceptable salt if from an acid (see col.6 lines 65+) as in claim 20 having a physical form of a cream (see col. 14, lines 1+)as in claim 21.

As to claims 7-9, the reference teaches the benzoquinolizine –2- carboxylic acid comprises 0-1to 10% of the compound (see col. 15, lines 1-6)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

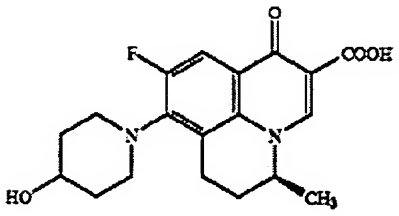
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 12 and 20-21 are rejected under 35 U.S.C. 103(a) as being obvious over de Souza et al. US 6,514,986 in view of de Souza et al. US 6,608,078 B2.

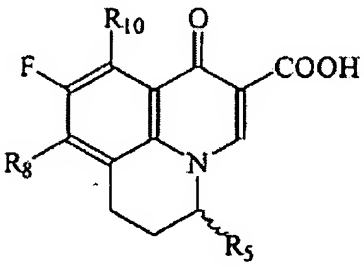
The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an

invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

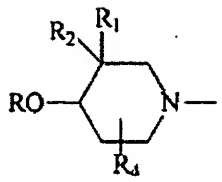
De Souza et al. teach a stable pharmaceutical composition comprising an aqueous carrier having in solution therein a benzoquinolizine-2-carboxylic acid



having the core chemical structure



as that disclosed in the instant claim1 (see col. 4, lines 15+) that is an optical active isomer, in a pharmaceutically acceptable salt arginine singly or combined with other antibacterial agents (see col. 8, lines 32+). With regards

to claim 2 R_5 is CH_3 and R8 is  is shown in the above structure, where R_1, R_2 R_4 are hydrogen. As to claims 3 and 6 the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin- 1-yl)-5-methyl- 1-oxo- 1H,5H- benzo(ij)quinolizine-2-carboxylic acid and the arginine salt form in claim 4 (see col. 5 lines 20+), where in the drug is 0.2 hydrate is obvious since the hydrate forms are from 0 to 1.0(see col. 4 lines 30) as in current claim 5 wherein the pharmaceutically acceptable salt if from an acid (see col. 2, lines 1+) as in claim 20 having a physical form of a cream (see col. 8, lines 35+)as in claim 21.

With regards to claim 1, the reference teaches a stable pharmaceutical composition having the core structure of the claimed invention (see col. 5, lines 25+), with the substituent or a polymorphs and pseudopolymorphs (see abstract) as in claim 1and 4, wherein the benzoquinolizine-2-carboxylic acid antimicrobial drug is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin- 1-yl)-5-methyl- 1-oxo- 1H,5H-benzo(ij)quinolizine-2-carboxylic acid and the arginine salt form in claim 4 (see col. 8 lines 11+) wherein the pharmaceutically acceptable salt if from an acid (see col.6 lines 65+) as in claim 20 having a physical form of a cream (see col. 14, lines 1+)as in claim 21.

As to claims 7-9, the reference teaches the benzoquinolizine –2- carboxylic acid comprises 0-1to 10% of the compound (see col. 15, lines 1-6)

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the above taught composition for the purpose of treating bacterial infections having the above-cited reference. Although, the combined references did not expressly state the kind of antibacterial agent to be used, one of ordinary skill in the art would be motivate to choose any of the antibacterial agents in the claimed invention as expect a successful result in doing so because these agents are well know as antibacterial agents and have been used in many formulation. Also it would be of knowledge to one of skill in the art to add a one of the claimed compounds of claims 12 to treat a disease that has a bacterial infection together with the claimed drug.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

Claims 1-21 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ardin H. Marschel 9/18/06

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

SVG
9/14/06